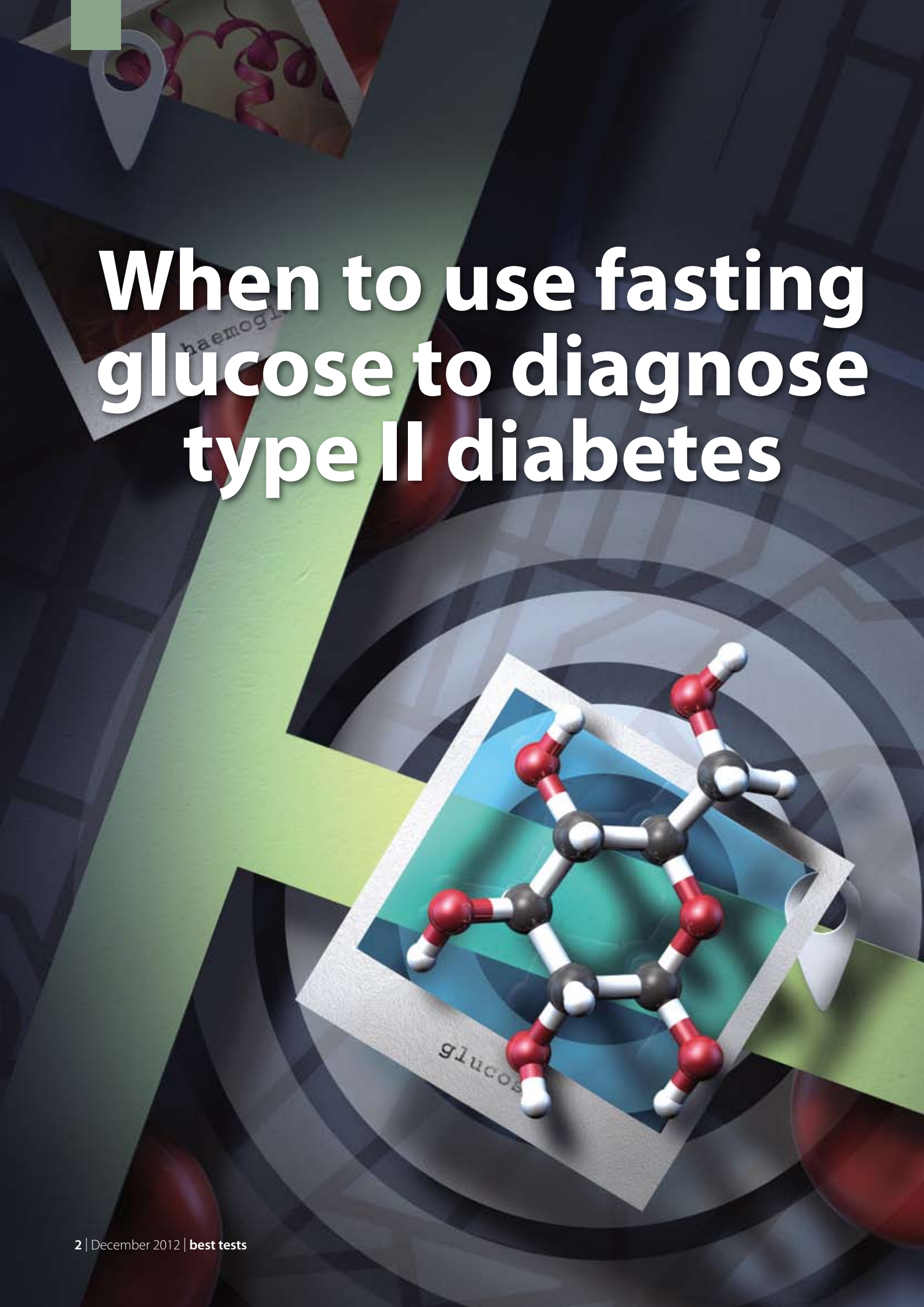
# When to use fasting glucose to diagnose type II diabetes



Until recently, fasting plasma glucose, and in some situations, oral glucose tolerance testing, have been the investigations of choice for diagnosing people with type II diabetes. Recently, recommendations in New Zealand have changed and $HbA_{1c}$ has become the primary assay for diagnosing type II diabetes, along with its continued role in monitoring glycaemic control. Other countries, such as the UK, USA and Australia, have also recently placed more importance on the use of $HbA_{1c}$ in diagnosing type II diabetes. However, there are some clinical scenarios where $HbA_{1c}$ is unreliable, and fasting plasma glucose should be used in preference.

## $HbA_{1c}$ is the recommended test for diagnosing type II diabetes in most situations

In September, 2011, the New Zealand Society for the Study of Diabetes (NZSSD) changed its recommendation regarding choice of test for diagnosing type II diabetes, stating that glycated haemoglobin ($HbA_{1c}$) was the preferred test over fasting glucose.[1] In addition, it is now recommended that $HbA_{1c}$ is the test of choice for population screening programmes.[2] However, there are some scenarios where measuring $HbA_{1c}$ for diagnostic purposes may give misleading or inaccurate results (see bullet list and Table 1 over page), and therefore a fasting plasma glucose is recommended.[1] Oral glucose tolerance testing (OGTT) is no longer recommended for most people as a test for type II diabetes.[2] N.B. OGTT is still used for diagnosis of women with gestational diabetes.

For further information on the change in guidance and the use of $HbA_{1c}$, see: "The new role of $HbA_{1c}$ in diagnosing type 2 diabetes", BPJ 42 (Feb, 2012), and "Understanding the new $HbA_{1c}$ units for the diagnosis of Type 2 diabetes" Braatvedt G et al, NZMJ 2012;125(1362).

## $HbA_{1c}$ results may be misleading in some people and situations

Fasting plasma glucose should only be used to test for type II diabetes in situations when the use of $HbA_{1c}$ is inappropriate.[1] The two primary situations where $HbA_{1c}$ may be inaccurate are when serum glucose levels have risen too quickly for glycation rates to provide an accurate picture, or where a condition is present that will affect the accuracy of $HbA_{1c}$ over the long term. Where serum glucose

## The inter-test variability between $HbA_{1c}$ and fasting glucose

When choosing the most appropriate diagnostic test for people with suspected type II diabetes, it is important that practitioners understand the limitations of each test.

Multiple studies have shown that $HbA_{1c}$ and fasting plasma glucose tests are frequently discordant when used to diagnose type II diabetes.[3] In some populations, such as Indo-Asian people, $HbA_{1c}$ diagnostic cut-off levels of 48 mmol/mol (a lower threshold than is used in New Zealand) identify fewer individuals as having type II diabetes than glucose-based tests.[3] However, in the majority of study populations this discordance is minor, and $HbA_{1c}$ and fasting plasma glucose generally identify similar numbers of people with diabetes.[4] In addition, the convenience of $HbA_{1c}$ testing is thought to significantly increase the absolute number of people diagnosed with type II diabetes, making it a more effective test for screening populations. $HbA_{1c}$ may not accurately reflect levels of glycaemic control in some situations or individuals (over page), but in comparison with fasting plasma glucose, it has greater analytic stability and less daytime variability in any individual patient, as well as far less stringent patient requirements, particularly the lack of required fasting.

has risen quickly, $HbA_{1c}$ should not be used. In clinical situations where $HbA_{1c}$ may be misleading, measuring glycation rates may still be useful, although consideration should be given to using fasting plasma glucose.

**Where serum glucose levels have risen rapidly, do not use $HbA_{1c}$**

A recent UK consensus statement recommended that $HbA_{1c}$ should not be used in the following patients or situations where blood glucose levels may have risen too fast to affect $HbA_{1c}$:[5]

- All children and young people or anyone with suspected type I diabetes, regardless of age
- People with a short duration of diabetes symptoms
- Women who are pregnant or have been pregnant in the previous two months
- People at high risk of diabetes who are acutely unwell ($HbA_{1c} \geq 50$ mmol/mol confirms pre-existing diabetes, but a value < 50 mmol/mol does not exclude it in an unwell patient and such patients should be retested once the acute episode has resolved)
- People taking medicines that may cause rapid glucose rise, e.g. corticosteroids or antipsychotics (for two months or less). $HbA_{1c}$ can be used in people taking such medicines long-term (over two months) who are not clinically unwell.
- People with acute pancreatic damage or who have had pancreatic surgery

In these situations, where symptoms have only been present for a short period (less than three months) and glycation of haemoglobin is unlikely to have occurred, it is more appropriate to request fasting plasma glucose than $HbA_{1c}$.[5] In addition, in some clinical settings self-monitoring blood glucose (SMBG) measurement, may be indicated to establish glucose levels to guide an acute intervention, such as hospital admission, in patients with suspected hyperglycaemia.

**In clinical conditions where $HbA_{1c}$ may be misleading, use with caution**

Certain clinical conditions may also affect the accuracy of an $HbA_{1c}$ test – the $HbA_{1c}$ may be falsely low and lead to false-negative results, or falsely elevated and lead to a false-positive result for type II diabetes. Some conditions have variable effects on $HbA_{1c}$ results and may increase or decrease $HbA_{1c}$ levels. Table 1 lists the most common conditions and factors that affect $HbA_{1c}$. $HbA_{1c}$ may still be useful in these situations, but it should be used with caution, and consideration given to using fasting plasma glucose.

These conditions need to be viewed within the clinical context of the patient. For many, the degree of effect on $HbA_{1c}$ results is modest. For example, iron deficiency tends to modestly raise $HbA_{1c}$ for unknown reasons.[11] However, if the rate of blood loss is enough to cause anaemia then $HbA_{1c}$ will typically fall due to increased red blood cell turnover, i.e. $HbA_{1c}$ will be falsely low, rather than high. A similar situation exists with patients who undergo venesection for haemochromatosis where $HbA_{1c}$ results can be very low. In general, $HbA_{1c}$ will still be useful, however, results should be viewed with caution and when there is clinical suspicion about the validity of the $HbA_{1c}$ result, discussion with a clinical biochemist (pathologist) may be appropriate.

Note that there is also a possible age-related effect when using $HbA_{1c}$, which rises approximately 0.3% each decade in people with normal glucose tolerance.[12] This does not limit the use of $HbA_{1c}$ in older people, but clinicians should be aware of the possible effect.

**Where $HbA_{1c}$ results are borderline** or further investigation of the result is necessary, such as in a patient with two discrepant $HbA_{1c}$ results, a fasting plasma glucose test may be useful if the result would change the management of the patient. However, waiting six months before retesting $HbA_{1c}$, with lifestyle interventions in the interim, would generally be the recommended management strategy.

## Fasting plasma glucose as a diagnostic test for type II diabetes

If a fasting plasma glucose test is indicated, rather than $HbA_{1c}$, this can be undertaken and interpreted in accordance with previous type II diabetes testing guidance.

Patients are required to fast (i.e. no caloric intake) for at least eight hours, but ideally 12 hours, prior to testing.[13] Advise patients that they may drink water during the fasting period.

**Table 1:** Factors influencing $HbA_{1c}$ results, modified from Gallagher[6,7]

| | $HbA_{1c}$ result | | |
|---|---|---|---|
| **Factor** | **Increased** | **Decreased** | **Variable** |
| **Red Cell Survival** (erythropoiesis) | Iron deficiency<br>Vitamin B12 deficiency<br>Renal impairment<br>Alcoholism | Iron supplementation<br>Vitamin B12 or folate supplementation<br>EPO treatment<br>Reticulocytosis<br>Chronic liver disease | Iron deficiency anaemia[8–10] |
| **Erythrocyte destruction or removal** | Splenectomy | Blood loss<br>Splenomegaly<br>Rheumatoid arthritis<br>Certain medicines, e.g. antiretrovirals, dapsone<br>Some haemoglobinopathies | |
| **Glycation rate** | Vitamin C or E deficiency<br>Some haemoglobinopathies<br>Chronic kidney disease | | Some genotypes, e.g. sickle cell disease |
| **Altered haemoglobin** | | Recent blood transfusion (previous three months)[1] | Some haemoglobinopathies<br>Methaemoglobin |
| **Assays** | Hyperbilirubinaemia<br>Carbamylated haemoglobin<br>Alcoholism<br>Aspirin (large doses)<br>Chronic opiate use<br>Hydroxyurea | | Some haemoglobinopathies |

**In symptomatic people** a single fasting plasma glucose result of ≥7.0 mmol/L can be considered diagnostic of type II diabetes for the majority of people.[1] Repeat testing is recommended where the result is borderline or there is clinical doubt about symptoms.

**In asymptomatic people** a fasting plasma glucose result of ≥7.0 mmol/L strongly indicates type II diabetes; however, a second test is required for confirmation.[1] The test should be performed on a separate occasion,[13] ideally within two weeks.[5] Lifestyle interventions should be encouraged during the waiting period. If the second result is discordant, repeat testing again in three to six months is recommended, with lifestyle interventions continuing in the interim.

## The disadvantages of fasting plasma glucose as a diagnostic test for type II diabetes

The fasting plasma glucose test has several disadvantages, many of which contributed to the NZSSD and WHO decisions to recommend that $HbA_{1c}$ be used as the preferred test for the diagnosis of type II diabetes.[1, 6]

The primary disadvantage of fasting plasma glucose is that it **requires the patient to fast** prior to testing, which can be difficult in practice.

The diagnostic range of fasting plasma glucose is narrow compared with the **biological variation** between individuals when tested with fasting glucose, which is

## The diagnostic criteria for type II diabetes[1]

| $HbA_{1c}$ * | Fasting glucose* | Diagnosis | Comments |
|---|---|---|---|
| ≥50 mmol/ mol, with symptoms | ≥7.0 mmol/L, with symptoms | Diabetes | |
| ≥50 mmol/ mol, no symptoms | ≥7.0 mmol/L, no symptoms | Diabetes | A second test above the threshold, with either fasting glucose or $HbA_{1c,}$ is required to confirm diagnosis |
| 41 – 49 mmol/mol | 6.1 – 6.9 mmol/L | Intermediate hyperglycaemia | Offer lifestyle advice. Perform CVD risk assessment and follow guidelines for treatment.<br>Repeat testing every 6 –12 months |
| ≤40 mmol/mol | ≤6.0 mmol/L | Diabetes unlikely<br>(normoglycaemia) | Normal range<br>Repeat testing at next CVD assessment or when clinically indicated |

* Requesting both $HbA_{1c}$ and fasting plasma glucose together in at-risk, asymptomatic people is unnecessary and discouraged.[5] However, if $HbA_{1c}$ and fasting plasma glucose are measured together, and results are discrepant with regards to a diagnosis of diabetes, the test above the diagnostic cut point should be repeated after three to six months.[1]

approximately 4.5%.[14] This means that if a group of patients have a fasting plasma glucose level of 7.0 mmol/L, most will have an actual value between 6.7 – 7.3 mmol/L (4.5% biological variation), but some will have a value outside of this range. Given the narrow diagnostic range for diabetes, with fasting plasma glucose, this can be significant.

The **sample processing** of fasting glucose is more complex than for $HbA_{1c}$, leading to a greater potential for errors. Variation can be up to 1 mmol/L or more after one to two hours, with an average of approximately 0.4 – 0.5 mmol/L (even if a fluoride tube is used).[15] When added to the biological variation, this difference can have a significant effect on the diagnostic accuracy of the test.

The **reproducibility of fasting plasma glucose** is lower than $HbA_{1c}$. An abnormal or borderline $HbA_{1c}$ result is far more likely to be abnormal on repeat than a borderline fasting glucose result.[16]

Fasting plasma glucose has an inferior **ability to predict long-term** outcomes, particularly beyond 15 years.[17]

## Monitoring patients where the use of $HbA_{1c}$ is misleading

All people with type II diabetes should have regular follow-up in general practice to monitor glycaemic control, risk level and disease progression. $HbA_{1c}$ is the recommended test for measuring glycaemic control during follow-up. In the presence of the co-morbidities discussed in Table 1, $HbA_{1c}$ may not accurately reflect the level of glycaemic control. Alternative methods for assessing control may be more appropriate, such as fasting plasma glucose and a series of self-monitoring blood glucose measurements for people using insulin. If therapeutic changes are being considered and there is clinical concern of the validity of the $HbA_{1c}$ test, discussion with a diabetologist is recommended. Measurement of fructosamine may be an alternative option for some people, however, the availability of this test varies, so it should be discussed with a clinical pathologist or diabetologist first. Fructosamine is a glycated protein that indicates glycation levels over the preceding 14 – 21 days.[18]

### How regularly should follow-up occur

Follow-up of people with type II diabetes should occur at least annually. In people with multiple co-morbidities

## Who should be screened for type II diabetes?

Current recommendations are for asymptomatic men aged over 45 years and women aged over 55 years to be screened for type II diabetes as part of a joint diabetes/cardiovascular risk assessment. Screening of asymptomatic Māori, Pacific and Indo-Asian people should begin at age 35 years for men and age 45 years for women.

Screening should be undertaken every three to five years depending on risk.

New Zealand Guidelines recommend screening ten years earlier in people with multiple risk factors:[1]

- A family history of early onset type II diabetes (more than one first-degree relative)*
- A history of gestational diabetes*
- Known ischaemic heart disease, cerebrovascular disease, or peripheral vascular disease*
- Central obesity or increased BMI (BMI > 30 or >27 kg/m$^2$ for Indo-Asian people)*
- Long-term steroid or antipsychotic treatment*
- Intermediate hyperglycaemia on previous assessment, e.g. $HbA_{1c}$ 41 – 49 mmol/mol or fasting plasma glucose 6.1 – 6.9 mmol/L
- An adverse lipid profile, e.g. TC/HDL ratio ≥7.0
- High blood pressure, e.g. ≥160/95 mm Hg
- Polycystic ovary syndrome
- Current smoker (or have quit within the last twelve months)

NZSSD also recommends that children and young adults with BMI >30 (or >27 kg/m$^2$ in Indo-Asian children) should be screened if:

- There is a family history of early onset type II diabetes or;
- They are of Māori, Pacific or Indo-Asian ethnicity

* Screening should be undertaken from age 25 years in people with multiple high risk factors, as indicated

## PHO Performance Indicators for diabetes

There are currently two PHO Performance Programme (PPP) indicators involving diabetes; diabetes detection and diabetes follow-up after detection. Both of these indicators are still active under the new funding scheme for diabetes: the Diabetes Care Improvement Package.

The purpose of the **diabetes detection** PPP indicator is to determine what proportion of the PHO population estimated to have diabetes has been diagnosed.[20]

The Indicator comprises 7.5% of a PHO's performance payment, with 2.5% for achieving the target in the total eligible PHO population and 5% in the high needs population.

The purpose of the **diabetes follow-up after detection** PPP indicator is to determine what proportion of the PHO population expected to have diagnosed diabetes has had a diabetes annual review.[20]

The Indicator comprises 9% of a PHO's performance payment, with 3% for achieving the target in the total eligible PHO population and 6% in the high needs population.

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or where regular medicine adjustments are being made to achieve appropriate control, more frequent consultations and testing e.g. three to six monthly, should be considered.

A full list of risk factors and the regularity of required follow-up can be found in the "New Zealand Primary Care Handbook 2012", available from: **www.health.govt.nz/publication/new-zealand-primary-care-handbook-2012**

Follow-up should include measurement of $HbA_{1c}$ (or an alternative method when $HbA_{1c}$ is not appropriate), blood pressure and lipid levels, an assessment of diabetes related complications including cardiovascular disease (CVD) risk assessment, kidney disease assessment and checks for foot and retinal complications.[19] In addition, educational material and advice on diet, exercise and smoking cessation should be discussed and provided at each follow-up visit, as applicable. N.B. Some factors, e.g. retinopathy will only need to be assessed annually, even in the highest risk groups.

### References

1. New Zealand Society for the Study of Diabetes. NZSSD position statement on the diagnosis of, and screening for, Type 2 diabetes. NZSSD; 2011. Available from: www.nzssd.org.nz (Accessed Dec, 2012).

2. Braatvedt G, Cundy T, Crooke M, Et al. Understanding the new HbA1c units for the diagnosis of Type 2 diabetes. NZ Med J 2012;125(1362):In press.

3. Malkani S, Mordes J. Implications of using hemoglobin A1c for diagnosing diabetes mellitus. Am J Med 2011;124(5):395–401.

4. Carson A, Reynolds K, Fonseca V, Muntner P. Comparison of A1c and fasting glucose criteria to diagnose diabetes among U.S. adults. Diabetes Care 2010;33(1):195–7.

5. John W. Expert position statement: Use of HbA1c in the diagnosis of diabetes mellitus in the UK. The implementation of World Health Organization guidance 2011. Diabet Med 2012;29:1350–7.

6. World Health Organisation (WHO). Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. WHO, Geneva; 2011. Available from: www.who.int/diabetes/publications/report-hba1c_2011.pdf (Accessed Dec, 2012).

7. Gallagher E, Le Roith D, Bloomgarden Z. Review of hemoglobin A1c in the management of diabetes. J Diabetes 2009;1:9–17.

8. Arnold J, McGowan J. Delay in diagnosis of diabetes mellitus due to inaccurate use of hemoglobin A1c levels. J Am Board Fam Med 2007;20(1):93–6.

9. Scottish Intercollegiate Guidelines Network (SIGN). Management of diabetes. SIGN; 2010. Available from: www.sign.ac.uk (Accessed Dec, 2012).

10. Clinical Enquiry and Response Service (CLEAR). Does iron deficiency or anaemia affect the HbA1c test in diabetic patients, particularly those with chronic kidney disease? NHS, Scotland; 2010. Available from: www.knowledge.scot.nhs.uk (Accessed Dec, 2012).

11. Kim C, Bullard K, Beckles G. Association between iron deficiency and A1c levels among adults without diabetes in the National Health and Nutrition Examination Survey, 1999-2006. Diabetes Care 2010;33(4):780–5.

12. Pani L, Korenda L, Et al. Effect of aging on A1c levels in individuals without diabetes: evidence from the Framingham Offspring Study and the National Health and Nutrition Examination Survey 2001-2004. Diabetes Care 2008;31(10):1991–6.

13. American Diabetes Association. Executive summary: Standards of medical care in diabetes 2012. Diabetes Care. 2012;35(Supplement 1):S4 –10.

14. Westgard QC. Desirable biological variation database specifications. Westgard; 2012. Available from: www.westgard.com/biodatabase1.htm (Accessed Dec, 2012).

15. Bruns D, Knowler W. Stabilization of glucose in blood samples: why it matters. Clin Chem 2009;55(5):850–2.

16. Selvin E, Crainiceanu C, Brancati F, Coresh J. Short-term variability in measures of glycemiz and implications for the classification of diabetes. Arch Intern Med 2007;167(14):1545–51.

17. Selvin E, Steffes M, Zhu H, Et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Eng J Med 2010;362:800–11.

18. American Diabetes Association. Fructosamine test. ADA, USA; 2012. Available from: http://professional.diabetes.org/Disease_Backgrounder.aspx?TYP=6&MID=262 (Accessed Dec, 2012).

19. New Zealand Gudelines Group. New Zealand primary care handbook 2012. 3rd ed. Wellington: New Zealand Guidelines Group; 2012.

20. DHBNZ. PHO Performance Programme. Indicator definitions. Version 5.5. 2012. Available from: www.dhbnz.org.nz/Site/SIG/pho/Operational-Documents.aspx (Accessed Dec, 2012).